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SUGHRUE MION, PLLC				
2100 PENNSYLVANIA AVENUE, N.W.				
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ART UNIT		PAPER NUMBER		
1623				
NOTIFICATION DATE		DELIVERY MODE		
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

sughrue@sughrue.com

PPROCESSING@SUGHRUE.COM

USPTO@SUGHRUE.COM

Office Action Summary

Application No.

10/577,154

Applicant(s)

KITAZONO ET AL.

Examiner

BAHAR SCHMIDTMANN

Art Unit

1623

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 07 February 2011.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-9 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-9 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 07 February 2011 has been entered.

This Office Action is in response to Applicant's Amendment and Remarks filed on 07 February 2011 in which claim 9 was newly added.

Claims 1-9 are pending in the current application and are examined on the merits herein.

The Declaration of Mr. Hiroaki Kaneko, submitted by Applicant on 07 February 2011 under 37 CFR §1.132 are acknowledged and will be further discussed below.

Modified Rejections

The following are new ground(s) or modified rejections necessitated by Applicant's amendment, filed on 07 February 2011, wherein claim 9 was newly added. Therefore, rejections from the previous Office Action, dated 04 March 2010, have been modified and are listed below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Katsukiyo et al. (US Patent No. 5,733,892, cited in previous Office Action) in view of Shigehisa et al. (JP 06-072893, cited in previous Office Action).

Katsukiyo et al. teaches compounds prepared by linking glycosaminoglycan to phospholipid or lipid (abstract). Examples 4 and 5 provide for the preparation of L-(α -phosphatidyl)ethanolamine dipalmitoyl-linked glycosaminoglycans (GAG-PPEADP). Specifically, Lot No. 1000 provides for the compound HA1-PPEADP (columns 47-50, tables L and M). Katsukiyo teaches their use as metastasis inhibitors, and as a part of a

composition with a pharmaceutically acceptable carrier (claim 1). Katsukiyo et al. teaches water as a pharmaceutically acceptable carrier (column 35, lines 21-25).

Katsukiyo et al. teaches the contents of phospholipid or lipid portions in the phospholipid- or lipid-linked glycosaminoglycans represented by formula (VIII) may range from 0.005 to 50% (column 34 lines 40-44). Applicant's disclosure of hydrogel includes the use of 1 to 100 equivalents of phosphatidyl ethanolamine based on 100 equivalents of the carboxyl group of hyaluronic acid (specification, column 6 lines 22-35 and column 7 lines 1-13). The range presented by Katsukiyo et al. is within the range provided in the disclosure.

Katsukiyo et al. also teaches the injectable solutions of the salt forms of the phospholipid- or lipid-linked glycosaminoglycan (column 35, lines 1-3). A syringe containing said injectable solution can be considered as a molded form of hyaluronic acid.

Katsukiyo et al. does not expressly disclose the embodiment of phosphatidyl ethanolamine where the acyl groups are unsaturated (instant claims 1-5). Katsukiyo et al. does not expressly disclose the phosphatidyl ethanolamine group conjugated at the C-6 position of hyaluronic acid (instant claims 1-8). Katsukiyo et al. does not expressly disclose the molded form as a non-woven cloth or film (instant claim 9).

Shigehisa et al. teaches an antirheumatic compound which uses lipid conjugates of glycosaminoglycans or its salts

Shigehisa et al. teaches that lipid-binding GAG weakens the inflammation of synovial tissue, i.e. the lipid-binding GAG reduces the neoplasia (metastasis) of a

synovial cell, fibrin deposition, the coagulation of lymphocytes, as well as prevent the extension of pannus involved in rheumatism (paragraph 0100). Shigehisa et al. teaches the binding of the carboxylic acid functional group of uronic acid in a glycosaminoglycan with the amine group of a lipid (paragraph 0016, chemical formula 1, C). Shigehisa et al. also teaches that the glycosaminoglycan used can be hyaluronic acid (paragraph 0020) and that the chain length and degree of unsaturation of an acyl group in a lipid are not limited (paragraph 0021). Shigehisa et al. teaches that phospholipid modified GAGs can be administered by intraarticular injection by mixing the compound in water, as well as by various other forms of administration to the synovial cavity, i.e. joints (paragraphs 0057, 0059, 0066). Shigehisa et al. teaches administering the GAGs to mice (paragraph 0065). Shigehisa et al. teaches the lipid-bound GAG can be formulated into liquid, solid or semi-solid dosage forms for various forms of administration (paragraph 0057). Shigehisa et al. teaches the lipid-bound GAGs may be formulated into tapes by kneading it with an adhesive and then spreading the mixture on a non-woven fabric (paragraph 0061). .

It would have been obvious at the time the invention was made to modify the 6-position of hyaluronic acid with dioleoylphosphatidyl ethanolamine and to administer this compound into the joint of a patient.

Based on the teachings of the MPEP and KSR cited in the previous Office Action, by employing the rationale in (G) some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention; one having

ordinary skill in the art would have been motivated to modify the 6-position of hyaluronic acid with dioleoylphosphatidyl ethanolamine and to administer this compound into the joint of a patient. Both Katsukiyo et al. and Shigehisa et al. teach that phospholipid modified glycosaminoglycans are useful in inhibiting metastasis. In addition to generally inhibiting metastasis, Shigehisa et al. teaches that phospholipid modified glycosaminoglycans can specifically inhibit metastasis (neoplasia) in the synovial cavity of joints and treat conditions such as rheumatoid arthritis. Therefore, because the phospholipid modified GAGs taught by Shigehisa et al. is used for similar purpose as that taught by Katsukiyo et al., one having ordinary skill in the art would have been motivated to modify the dipalmitoylphosphatidyl ethanolamine to have a single degree of unsaturation, i.e. dioleoylphosphatidyl, for administration into joint.

Additionally, Shigehisa et al. teaches the lipid-bound GAGs can be molded into a tape which is then spread onto a non-woven fabric. Upon drying, the composition would take the form of a film and/or the form of the object itself, i.e. the non-woven fabric since the composition becomes integrated as a part of the non-woven fabric. Thus, one having ordinary skill in the art would have been motivated to prepare a molded form of the instantly claimed compound as a film and/or non-woven cloth.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Response to Arguments

Applicant's arguments filed 07 February 2011 and the Declaration of Mr. Hiroaki Kaneko, submitted by Applicant on 07 February 2011 under 37 CFR §1.132 have been fully considered but they are not persuasive.

Applicant's experimental results regarding the hydrogel properties of hyaluronic acid modified with L- α -diplamitylphosphatidyl ethanolamine have been fully considered but they are not found persuasive.

Applicant has synthesized hyaluronic acid conjugated to phosphatidyl ethanolamine having a saturated C16 fatty acid, as taught by the prior art Katsukiyo. Applicant has argued and shown that this compound does not form a hydrogel, but instead forms a non-viscous liquid. Applicant contends that a hydrogel of the hyaluronic acid compound of the present invention has a high elastic modulus of 200 Pa or more.

The declaration of Mr. Hiroaki Kaneko teaches hyaluronic acid is reacted with 40 equivalents of L- α -diplamitylphosphatidyl ethanolamine to obtain a freeze-dried product. Applicant then mixes 30 mg of this freeze dried product in 970 mg of ion-exchange water, which Applicant describes as a non-viscous liquid at a concentration of 3 wt.%.

Applicant has argued that using the saturated C16 fatty acid as described by Katsukiyo et al. does not form a hydrogel, but rather a non-viscous liquid under the same conditions as in Example 1 of the present application.

Example 1 of Applicant's specification is directed towards modifying hyaluronic acid with 10 equivalents of L- α -dioleoylphosphatidyl ethanolamine (see page 8, example 1 of the instant specification) to obtain a freeze-dried product. Afterwards, 30 mg of this freeze dried product is dissolved in 970 mg of ion exchange water to prepare a hydrogel

having a concentration of 3 wt.% (p.9, lines 1-15). Example 2 of Applicant's specification is directed towards reacting 40 equivalents of L- α -dioleoylphosphatidyl ethanolamine with hyaluronic acid. The final products from examples 1 and 2 have an elastic modulus of 421 Pa and 902 Pa, respectively.

From Applicant's own examples provided and the Declaration of Mr. Hiroaki Kaneko, an aqueous solution comprising 3 wt.% of the freeze-dried product was prepared. From this one example, Applicant has concluded that the C16 saturated phosphatidyl ethanolamine conjugated to hyaluronic acid is not in fact a hydrogel, whereas an unsaturated C18 phosphatidyl ethanolamine at that concentration did form a hydrogel, and that the obviousness rejection should be withdrawn based on these differences.

it is noted that the features upon which applicant relies (i.e., 3 wt.% of the claimed compound in an aqueous medium) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The experimental result provided by Applicant is insufficient to show non-obviousness for the following reasons. Applicant has defined a hydrogel wherein 1 to 100 equivalents of phosphatidyl ethanolamine are reacted with hyaluronic acid, based on 100 equivalents of the carboxyl group of hyaluronic acid (specification, column 6 lines 22-35 and column 7 lines 1-13). It is well known to a person having ordinary skill in the art that formation of a hydrogel is directly dependent on how much water is mixed with a polymer. Therefore, it is still possible that the

product directly taught by Katsukiyo et al. forms a hydrogel at a different concentration in water.

Modification of the concentration is well within a person having ordinary skill in the art. A showing of only one concentration, which is not even a limitation of the instant claims, is not enough to negate the structural similarities between the two compounds, their shared functional utilities and the suggestion by Shigehisa to modify phosphatidyl ethanolamine to bear unsaturated alkyl groups to arrive at the instantly claimed invention.

It is even further noted that only instant claim 4 is directed towards a hydrogel, a term broadly encompassing a polymer dispersed in water at a concentration to form an aqueous-based gel. The scope of instant claims 6-8 encompasses hyaluronic acid conjugated to phosphatidyl ethanolamine bearing a saturated C16 alkyl group as a "joint treating material". As discussed in the obviousness rational above, and in the previous Office Actions, it would have been obvious to administer the compounds/compositions into the joint in view of Shigehisa et al.

With respect to the instant claims, there has been no clear comparison between the full scope and breadth of the claimed compositions. A demonstration of hydrogel having a high elastic modulus of 200 Pa or more is highly dependent on the concentration of the claimed compounds in water as well as the amount (i.e. equivalent of phosphatidyl ethanolamine, based on 100 equivalent of carboxyl group of hyaluronic acid) of phosphatidyl ethanolamine substituted on the hyaluronic acid.

Therefore, the evidence presented in specification and declaration herein is not seen to be clear and convincing in support the nonobviousness of the instant claimed invention over the prior art.

The rejection is hereby **maintained**.

Conclusion

In view of the rejections to the pending claims set forth above, no claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ms. BAHAR SCHMIDTMANN whose telephone number is 571-270-1326. The examiner can normally be reached on Mon-Thurs 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ms. Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/BAHAR SCHMIDTMANN/
Patent Examiner
Art Unit 1623

/Shaojia Anna Jiang/
Supervisory Patent Examiner
Art Unit 1623